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Aortic growth rates in a Swedish cohort of women with Turner syndrome☆

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ABSTRACT

Background: Aortic dilation, cardiac malformations and hypertension are known risk factors for aortic dissection in Turner syndrome (TS). In the current guidelines, rapid growth of the aorta has been added as a risk marker. This study aimed to estimate the growth of the ascending aorta over time, to identify risk factors of aortic growth, and to describe aortic complications in TS.

Methods: A transthoracic echocardiogram was performed at least twice in 101 women with TS, mean age 28 years, with a mean follow-up of 8.3 ± 3.4 (range 1–17) years. The investigator was blinded to the clinical status. Logistic regression analysis was used to identify risk factors of aortic growth.

Results: The prevalence of ascending aortic dilation (ASI >20 mm/m^2) was 26 % and the mean ascending aortic diameter was 27.0 ± 4.8 mm at baseline. Significant aortic growth was found at sinus of Valsalva 1.08 (±2.11) mm, sinotubular junction 1.07 (±2.23) mm, and the ascending aorta 2.32 (±2.93) mm, $p < 0.001$. The mean ascending aortic growth rate was 0.25 (±0.35) mm/year, and higher compared to the general female population, 0.12 (±0.05) mm/year, $p < 0.0001$. No risk factors for aortic growth (bicuspid aortic valve, coarctatio, hypertension or karyotype) other than body weight could be identified, Odds ratio 1.05 (95 % CI 1.00–1.09), $p = 0.029$. Eight women had an aortic event of whom all had bicuspid aortic valves.

Conclusions: The growth rate of the ascending aorta in TS was increased compared to the general female population. Congenital cardiovascular malformations were not predictive of aortic growth.

1. Introduction

Turner syndrome (TS) is a complex genetic disorder affecting 1/2500 live-born girls, and is caused by a complete or partial absence of one of the X chromosomes, (45,X) [1]. The syndrome is usually associated with short stature, gonadal dysfunction, and congenital cardiovascular malformations such as coarctation of the aorta (CoA) and bicuspid aortic valves (BAV) [2].

CoA, BAV, hypertension, and aortic dilatation are risk factors for aortic dissection, which is a rare but often catastrophic event and strongly contributes to the increased risk of early death in TS [3–5]. Once aortic dissection has occurred, mortality is 1–2% for each hour afterwards, resulting in a 48-h mortality of approximately 50 % [6]. In the current international guidelines for TS rapid progression of the aortic size (>5 mm over a one-year period) has been added as an additional risk marker [7,8]. The guidelines recommend consideration of prophylactic surgery on ascending aortic aneurysms in patients with an aggressive increase of the aortic diameter [9]. Studies have reported an average growth rate of the ascending aorta in TS to approximately 0.2 mm/year, in comparison to the general female population growth rate of 0.12 mm/year [10–15]. However, many of these studies have a small sample size or a short follow up time. The aims of this study were to estimate the growth of the ascending aorta over time, to identify risk factors of aortic growth, and describe aortic events in women with TS.

Abbreviations: ASI, aortic size index; TS, Turner syndrome; TTE, transthoracic echocardiogram.

☆ The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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2. Methods

2.1. Study design and ethical considerations

This was a single center, retrospective cohort study. Women who had at least two transthoracic echocardiograms (TTEs) from a previously published TS cohort were identified [16]. They were included between January 1995 and March 2021 at the Turner center in Gothenburg and were followed to the date of death or until February 2023. The study was approved by the Regional Ethical Review Board in Gothenburg and conducted in accordance with the Helsinki declaration [17]. All patients provided informed consent.

2.2. Participants

The inclusion criteria in this study were phenotypic subjects with cytogenetically confirmed Turner syndrome, ≥16 years of age, and at least two TTEs of the proximal aorta. An exclusion criterion for the growth analyses was aortic interventions prior to the first TTE or between the first and the last TTE. The patients were included in the study after transition from the pediatric clinics to the adult endocrine out-patient clinic.

2.3. Echocardiography and examinations

All patients were examined, the data including anthropometric measurements were anonymized, and included in a study database as previously described [16]. According to the current national and international guidelines for TS at the time of the study period, the patients underwent TTE at Sahlgrenska University hospital at least every 1–5 years depending on their risk profile for aortic dissection, (i.e. CoA, BAV, hypertension, and ascending aortic size), with a standardized follow up every 5th year in women with TS without mentioned risk profile [1,8,18,19]. Patients with any risk factor were followed at the Grown Up Congenital Heart (GUCH) out-patient clinic with an individualized program. Digital storing of TTEs became available in 2003 at Sahlgrenska University hospital. As a consequence, the patients' first TTE in this study could not be older than from 2003. Their first and last available TTE were identified, and measurements of the proximal ascending aorta dimensions were performed in 2023 by the same experienced operator with the same measurement criteria on a workstation (EchoPac PC, GE Healthcare, Chicago, IL, USA). The operator was blinded to the patient's clinical status, previous results and whether the recorded TTE was the patient's first or last examination, respectively.

The aortic variables were measured at four levels: aortic annulus, sinus of Valsalva, sinotubular junction and ascending aorta, with the use of the parasternal long axis view. The maximal diameter in diastole was measured from the inner edge to the inner edge of the aortic wall [20].

The growth rates were computed as the difference in aortic diameter between the first and the last echocardiogram, divided by the duration of follow-up. Like in other studies a negative aortic diameter change could therefore occur [10–12,21].

The aortic valve (bicuspid or tricuspid) and CoA were classified by TTE or magnetic resonance imaging (MRI) in accordance with clinical practice. Aortic dilatation was defined as an ascending aortic size, (ASI) ≥20 mm/m^2 according to international guidelines for Turner syndrome [8]. The ASI was computed by dividing the diameter of the ascending aorta by the body surface area. Body surface area (BSA) was calculated with the Du Bois method [22]. Aortic growth of the ascending aorta was defined as an increase of ≥2 mm between the first and the last TTE according to the measurement error of the method estimated by the repeatability coefficient (RC), described in the statistical section. Body mass index (BMI) was calculated as body weight divided by height in meter squared and expressed as kg/m^2. Waist circumference was measured in cm midway between the lowest rib and the iliac crest. Hip circumference was measured in cm at the widest part over the hip. Waist-to-height ratio and waist-to-hip ratio were used as proxies for central obesity and were calculated by dividing the waist circumference by the height and the hip measurement, respectively.

2.4. Genotype

The genotype was defined on the karyotype based on conventional cytogenetic analysis of ≥25 metaphases with a chromosome quality of 400 bands. Turner syndrome was defined as mosaic if > 5 % but <95 % of all cells demonstrated loss or partial loss of the second sex chromosome, and as monosomy if ≥ 95 % loss of the second sex chromosome was confirmed. This was based on the cytogenetic analyses (Fluorescence In Situ Hybridization or karyotype) of the buccal cells or the lymphocytes in blood. The lower limit was defined in accordance with Homer et al. [23].

2.5. Statistical analysis

Kolmogorov-Smirnov test was used to test the variables distribution. Normally distributed continuous variables were described with means and standard deviations (SD) and non-normally distributed continuous variables with medians and interquartile range (IQR). For comparison between groups, Fisher's Exact test was used for dichotomous variables and the Mann-Whitney *U* test for non-normally distributed continuous variables. Aortic diameters at first and last echocardiogram were compared with Wilcoxon signed-rank test. Unpaired *t*-test was used to compare the estimated aortic growth rates with the growth rates of the population and Fisher's non-parametric permutation test was used to compare the growth rates between groups. Correlation was tested with the non-parametric Spearman's correlation test. Odds ratios with 95 % confidence intervals were calculated using logistic regression analysis and the analyses were adjusted for age. Firth's penalized maximum likelihood estimation was used to reduce bias in parameters with low numbers.

To evaluate the methodological measurement error, we performed a test-retest procedure. Two different investigators acquired the recording necessary for measurement of the ascending aorta diameter with the second investigator blinded to the images of the first recording. The same observer measured the ascending aorta from the two different recordings using the same measurement procedure and measuring system. The observer was blinded to the results of the first measurement when performing the second measurement. Test-retest reliability of the TTEs was estimated by calculating the repeatability coefficient (RC) with formula $1.96x\sqrt{\Sigma(m2-m1)2/n}$, in 30 patients (60 examinations were performed), and the measurement error was estimated to 1.9 mm [24].

All tests were two-tailed and $p < 0.05$ was considered significant. All analyses were performed using either SPSS version 24.0 for Windows (IBM, Armonk, NY, USA) or SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Study cohort demographics

In total 118 women with TS were eligible of whom five patients were excluded from the analyses of growth due to aortic interventions during follow-up (Supplementary Table 1) and 12 patients were excluded due to poor quality of the TTE. The remaining 101 women with TS were included in the study of growth. Some of the aortic diameters between the first and the last TTEs could not be remeasured and were therefore not included in the analyses. Thus, 100 women had at least two available measurements of the aortic annulus, 101 of the sinus of Valsalva, 89 of the sinotubular junction, and 77 of the ascending aorta.

The average age of the total cohort with TS at the time of inclusion

was 28 years, ranging from 16 to 57 years. 14/101 (14 %) of the patients had a BMI >30 kg/m^2. The median waist-to-height ratio was 0.51 ± 0.06 and the waist-to-hip ratio was 0.80 ± 0.06. None of the patients met the criteria for the metabolic syndrome as per the definition by the International Diabetes Federation [25]. BAV was found in 26/101 cases (25 %), CoA in 15/101 cases (15 %), and hypertension, defined as ≥140/90 mmHg or the use of blood pressure medication, in 12/101 cases (12 %). The mean time between the first and the last echocardiogram was 8.3 years (min 1, max 17 years). The average number of TTEs was 2.7 per individual, minimum 2, maximum 5. The mean ascending aortic diameter was 27.0 ± 4.8 mm. The prevalence of aortic dilatation (ascending aorta) at first TTE was (20/77) 26 % and at follow-up it had increased to (29/77) 38 %.

The patients were divided into two groups: growth of the ascending aorta (n = 38) or no growth ascending aorta (n = 39). The baseline characteristics including the frequencies of BAV, CoA and hypertension were similar in the two groups except for monosomy (45,X), that was more prevalent in the patients with no growth of the ascending aorta, Table 1.

Table 1
Baseline characteristics in women with Turner syndrome with and without growth of the ascending aorta.

	TS women with TTEs of the ascending aorta n = 77	TS women with no growth of the ascending aorta n = 38	TS women with growth of the ascending aorta n = 39	P value[a]
	Mean ± SD	Mean ± SD	Mean ± SD	
Age, years	27.6 ± 9.8	27.3 ± 8.9	27.9 ± 10.7	0.78
Height, cm	152.8 ± 7.2	152.1 ± 6.3	153.4 ± 8.1	0.42
Body weight, kg	58.1 ± 12.3	55.7 ± 9.8	60.5 ± 14.1	0.087
Body mass index, kg/m^2	24.8 ± 4.2	24.1 ± 3.5	25.5 ± 4.7	0.14
Waist-to-height ratio	0.51 ± 0.06	0.50 ± 0.06	0.51 ± 0.07	0.66
Waist-to-hip ratio	0.80 ± 0.06	0.80 ± 0.06	0.80 ± 0.06	0.84
Monosomy (45,X), n (%)	34 (44.2)	22 (57.9)	12 (30.8)	0.030
Ascending aorta, cm	27.0 ± 4.8	28.1 ± 5.2	26.0 ± 4.3	0.057
Bicuspid aortic valve, n (%)	21 (27.3)	9 (23.7)	12 (30.8)	0.66
Coarctatio aortae, n (%)	11 (14.3)	6 (15.8)	5 (12.8)	0.96
Systolic BP, mmHg	120.4 ± 14.6	118.3 ± 13.8	122.4 ± 15.2	0.22
Diastolic BP, mmHg	75.6 ± 9.7	74.0 ± 9.6	77.2 ± 9.7	0.15
GH therapy, n (%)	49 (63.6)	24 (63.2)	25 (64.1)	1.00
Estrogen HRT, n (%)	69 (92.0)	33 (91.7)	36 (92.3)	1.00
BP medication, n (%)	5 (6.7)	2 (5.6)	3 (7.7)	1.00
Total cholesterol, mmol/L	5.6 ± 5.5	6.19 ± 8.1	5.2 ± 0.9	0.87
Smoker, n (%)	8 (10.5)	5 (13.5)	3 (7.7)	0.65
Diabetes mellitus, n (%)	0 (0)	0 (0)	0 (0)	–

BP, Blood pressure; GH, growth hormone; HRT, hormone replacement therapy; TS, Turner syndrome. [a] P values are shown for comparisons between women with and without growth of the ascending aorta using the Mann-Whitney *U* test/ Fisher's Exact test.

3.2. Aortic growth rates

The mean ascending aortic growth rate of all women was 0.25 (±0.35) mm/year. Women with growth of the ascending aorta (≥2.0 mm between the first and last TTE) had a mean ascending growth rate of 0.49 (±0.25) mm/year.

Table 2 shows the growth and growth rates of the proximal aorta. The ascending aortic growth rate was normally distributed, the other levels were not. There was a significant growth at three of the four aortic levels: sinus of Valsalva, sinotubular junction and ascending aorta, $p < 0.001$. The growth rate of the ascending aortic diameter (0.25 ± 0.35 mm/year) was significantly increased compared to the general female population, 0.12 (±0.05) reported by Campens et al. $p < 0.0001$ [14].

There was a significant correlation, $r = 0.45$, $p < 0.0001$, between the ascending aortic diameter change and the time from the first to the last TTE (Fig. 1A). However, there was no acceleration of the ascending growth rate during the follow-up period as there was no correlation between growth rate and follow-up time (Fig. 1B).

3.3. Risk factors

Previously given growth hormone therapy or ongoing estrogen replacement therapy were not associated with aortic growth of the ascending aorta or aortic dilatation. Neither were risk factors for aortic dissection (CoA, BAV, hypertension, and 45,X). The Odds ratio (OR) for 45,X was 0.34 (95 % CI, 0.13–0.89) $p = 0.028$. Body weight was associated with growth of the ascending aorta, OR 1.05 (95 % CI, 1.0–1.09) $p = 0.029$, but not with aortic dilatation. Neither the waist-to-height ratio nor the waist-to-hip ratio, respectively, correlated with either the aortic size or growth of the ascending aorta.

The median growth rates of the aorta in women with different TS karyotypes are demonstrated in Table 3. The women with the deletions had the lowest growth rate of the ascending aorta and the women with Y-material the highest, but no conclusions could be drawn due to the small number of patients in each group.

Four women became pregnant during the time from the first to the last TTE. In total six children were born, all after oocyte donations. The median size of the ascending aorta was 25.3 (min 18.8, max 35.6) mm before the pregnancies. The median aortic growth rates and IQR in the pregnant women were estimated to: aortic annulus 0.00 (−0.03; 0.09) mm/year, sinus of Valsalva 0.14 (−0.04; 0.24) mm/year, sinotubular junction 0.12 (−0.02; 0.36) mm/year, and ascending aorta 0.45 (min 0.25, max 0.86) mm/year.

Table 2
Aortic diameters and growth rates of women with Turner syndrome.

Position	First TTE (mm)	Last TTE (mm)	p-value*	Mean change (mm)	Mean growth rate (mm/year)	Median growth rate (mm/year)
Aortic annulus n = 100	19.6 (±2.1)	19.7 (±2.1)	0.20	0.13 (±1.41)	0.003 (±0.22)	0.015 (−0.07; 0.12)
Sinus of Valsalva n = 101	28.1 (±3.3)	29.2 (±4.0)	<0.001	1.08 (±2.11)	0.13 (±0.33)	0.14 (−0.02; 0.29)
Sinotubular junction n = 89	24.2 (3.4)	25.3 (±4.0)	<0.001	1.07 (±2.23)	0.16 (±0.49)	0.075 (−0.03; 0.31)
Ascending aorta n = 77	27.0 (4.8)	29.3 (±5.3)	<0.001	2.32 (±2.93)	0.25 (±0.35)	0.25 (0.03; 0.44)

TTE, transthoracic echocardiogram; *P values were calculated by Wilcoxon signed rank test for comparison of first and last TTE. Mean presented with SD, median with IQR.

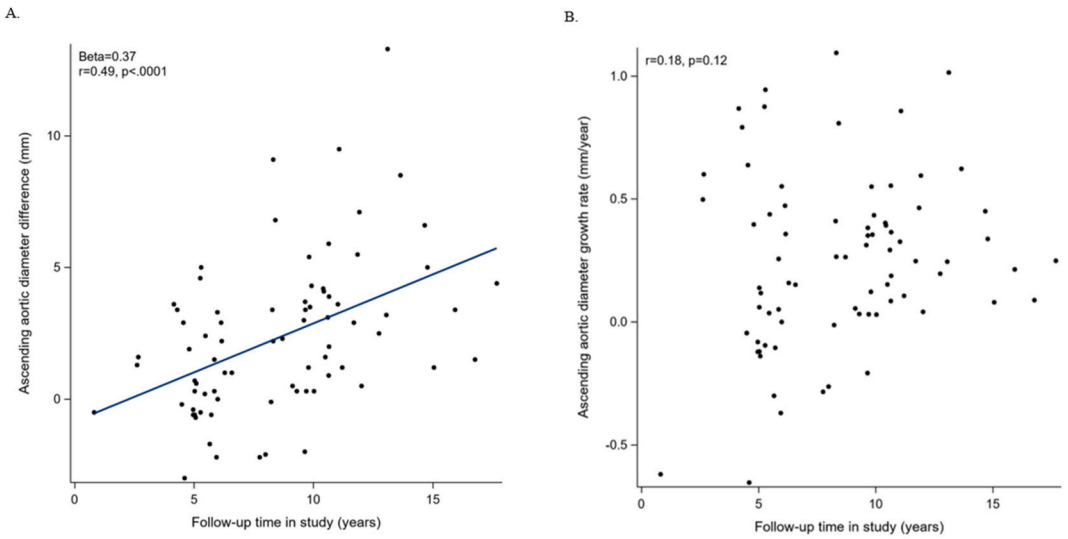

Fig. 1. Correlation between growth of the ascending aorta and time in 77 women with Turner Syndrome, aged 16–57 years. (A) Spearman's correlation coefficient (r_s) = 0.49, p=<0.001. (B) No acceleration of the ascending growth rate was found during follow-up during 1–17 years in Turner Syndrome, r_s = 0.18, p = 0.12.

Table 3
Median growth rates of the proximal aorta in women with different TS karyotypes.

Karyotype	Aortic annulus mm/year (IQR)	n	Sinus of Valsalva mm/year (IQR)	n	Sinotubular junction mm/year (IQR)	n	Ascending aorta mm/year (IQR)	n
45,X	0.013 (−0.08; 0.15)	45	0.19 (0.05; 0.029)	45	0.11 (−0.02; 0.045)	38	0.14 (−0.01; 0.34)	34
46,XX/45,X	0.041 (0.01; 0.11)	17	0.048 (−0.08; 0.15)	17	0.19 (0.02; 0.28)	15	0.37 (0.15; 0.55)	14
Iso chromosome	0 (−0.17; 0.04)	12	0.16 (−0.04; 0.46)	13	−0.006 (−0.16; 0.11)	13	0.36 (0.12; 0.64)	11
Ring chromosome	−0.017 (−0.06; 0)	5	0.084 (0.05; 0.10)	5	−0.004 (−0.11; 0.09)	4	0.18 (0.02; 0.4)	4
Y-material	0.065 (−0.86; 0.23)	8	0.20 (0.09; 0.27)	8	0.09 (−0.08; 0.21)	7	0.40 (0.19; 0.56)	6
Deletion	0.01 (−0.33; 0.15)	6	0.15 (0.09; 0.27)	6	−0.07 (−0.16; 0.34)	6	0.06 (0.05; 0.79)	6

N = number of patients. Karyotypes with less than 4 patients were excluded in the analyses.

3.4. Aortic events

Eight women with TS had an aortic event. Two patients suffered aortic dissections, of whom one was excluded from the study due to surgery prior to the first TTE [26]. The other patient was medically treated, and her growth rate of the ascending aorta was 0.6 mm/year during 11.9 years follow-up. Another patient with BAV died of a rupture of the aorta due to endocarditis. The highest growth rate of the ascending aorta was in a woman with aortic valve stenosis and aortic dilatation. She had a growth rate of the ascending aorta of 1.1 mm/year and underwent prophylactic surgery with composite aortic valve and root replacement after 8.3 years follow-up. The aortic growth rates of the other patients with aortic valve replacements were not available. BAV was found in all eight patients with aortic events, 100 %, and CoA was found in 50 % of those with aortic events, Supplementary Table 1.

4. Discussion

4.1. Aortic growth rates

This study was designed to estimate growth and growth rates of the proximal aorta in an adult population with TS and to study the risk factors for aortic growth in this population. There was a significant growth at three of the four aortic levels: sinus of Valsalva, sinotubular junction and ascending aorta, $p < 0.001$ until up to 17 years' of follow-up. The estimated mean growth rate of the ascending aorta in this study was 0.25 (±0.35) mm/year, which is similar to other studies with different modalities (MRI, CT, TTE) [10–13]. A recent study by Meccanici et al. reported a minimal mean growth of the ascending aorta of 0.03 (±0.60) mm/year. This may be explained by their short follow-up period of 3 years [21]. In the present study the growth rate of the ascending aorta (0.25 ± 0.35 mm/year) was approximately twice as fast as in the general female population, 0.12 (±0.05), $p < 0.0001$ [14]. However, Mortensen et al. concluded in a recent cardiovascular MRI study that aortic growth rates were not increased in TS. They reported similar growth rate of the ascending aorta, 0.20 (±0.35) mm/year, but their control group with a growth rate of the ascending aorta of 0.26 (±0.14) mm/year, consisted of only 37 individuals recruited by an advertisement, which may have affected the results [11]. In absolute terms, an increase of 0.25 mm per year is a minor increase and, may not be clinically relevant in the short run, but over a lifetime, aortic dilatation may develop in susceptible individuals.

With time the ascending aorta was growing wider in TS, $r = 0.45$, $p < 0.0001$, but the growth rate was not accelerating, Fig. 1. Using standardized protocols and the same modality for aortic measurements are crucial to ensure consistent and reliable data over time, enabling the detection of aortic growth while minimizing random errors. In clinical practice, TTE is the most commonly used technique for assessing the proximal aorta and facilitates aortic valve visualization. MRI is an excellent modality for aortic diameter measurements, offering detailed depictions of aortic shape and its relationship to adjacent structures [9,27,28]. Unlike CT, MRI does not involve ionizing radiation or contrast agents, making it suitable for serial examination but it is a costly option [29]. However, in cases with aortic dilatation the measurements are confirmed with CT/MRI and the decision of prophylactic intervention is always based on measurements derived from those multiple modalities [9].

The recommended frequency of monitoring in the guidelines vary

depending on aortic size and risk factors but are likely frequent enough to detect an aortic dilatation developing over time [7,8]. However, sudden catastrophic events such as aortic dissections/ruptures are harder to predict even with frequent examinations.

4.2. Risk factors

Previous studies have reported an association between BAV and aortic growth [11,21,30]. This could not be confirmed in this study. Neither were risk factors for aortic dissection such as CoA, hypertension, aortic dilatation, nor monosomy (45,X) of significance for aortic growth in the present study. However, body weight at baseline was associated with growth of the ascending aorta, OR 1.05 (95 % CI, 1.0–1.09) p = 0.029. The explanation for this is not known, but body weight has been strongly correlated with ascending aortic diameters in the general population and in TS [12,14]. One could only speculate that with increasing body weight, which in TS usually increase the abdominal fat distribution because of their short stature, a heavier burden and resistance for the cardiac output and the circulation appear [31]. However, the waist-to-hip ratio did not turn out to support this hypothesis although the waist-to-height ratio was mildly increased. Hypertension though, was not associated with or predictive of aortic growth in this study. Previously given growth hormone therapy was not associated with aortic growth of the ascending aorta, in accordance with a study by Bondy et al. [32].

The prevalence of aortic dilatation varies in different studies which may be explained by different definitions, imaging modalities and selection bias of more severely affected patients [15]. In women without TS, aortic dilatation is defined as ASI >22 mm/m^2, or an ascending aortic diameter >34 mm [33]. In the guidelines for TS, dilatation is defined as ASI ≥20 mm/m^2, accounting for the shorter stature in TS [8]. This definition has been widely adopted in numerous studies related to the condition [5,12,21,30,34–36]. In the present study, the prevalence of aortic dilatation of the ascending aorta at the first TTE was 25.9 %, which is similar to the pooled prevalence reported by Meccanici et al. in a systematic meta-analysis [15].

Monosomy (45, X) was the most frequent genotype in the study cohort (47 %), which is in line with previous litterature [8]. To the best of our knowledge there is no other study presenting growth rates of the proximal aorta in different TS karyotypes. Surprisingly, monosomy had the lowest growth rate of the ascending aorta and seemed protective for growth of the ascending aorta, OR 0.34 (95 % CI, 0.13–0.89). There is no obvious explanation for this finding as monosomy is usually associated with a more severe phenotype. Hence, no karyotype in TS can be foreseen as a high risk or protected for aortic growth due to the genotype.

During the study period four women became pregnant. As previously reported by Duijnhouwer et al. and Donadille et al. there was no significantly difference in growth rate from the rest of the cohort, but the number of patients is too low to draw any conclusions [12,30]. However, pregnant women with TS are at risk of aortic dissection and should always be followed thoroughly during pregnancy [8,16]. The patients in our study with aortic dilatation and all the pregnant women were monitored at the GUCH clinic with more frequent TTEs.

4.3. Aortic events

In this study there were a low number of incidental events; one aortic rupture and two aortic dissections. However, these cases contribute to a high prevalence of serious aortic events for TS, 3 %. Additionally, there were five elective aortic interventions: four aortic valve replacements and one supracoronary graft. All the eight patients had BAV in common, which poses a risk for aortic dilatation and dissection. Unfortunately, the aortic growth rates were only accessible for three of the patients, a sample size too small to draw any conclusions.

The TS guidelines contain flowcharts for regular cardiac monitoring and recommendations for prophylactic surgery at threshold values of the aorta to prevent aortic dissections [7,8]. In the general population most ascending aortic dissections occur without a prior aortic dilatation [37]. Even if aortic dilatation is a known risk factor for aortic dissection, it is still unclear whether women with TS and aortic dissection have a steady growth of the aorta over time to a point where it dissects or whether their aorta suddenly dissects without previous gradual growth.

The result of the present study showing a progress of the aortic width by time and age is of importance for the care of women with TS. Previous studies, trying to identify risk factors or predictors for aortic dissection, have found that aortic dilatation is one of the most important markers for the association with aortic dissection [4,5,38]. The present results contribute to a better understanding of the high risk of aortic dissection at a young age in TS. When designing cardiovascular surveillance programs to prevent aortic dissections, aortic measurement with focus on the diameter ought to be more specified at the echocardiography, which might be performed more often than every 5-10th year in patients without risk factors. A risk-score could be created in a larger sample of patients.

4.4. Strengths and limitations

The study consists of a relatively large cohort and a follow-up duration of 8.3 years, range 1–17 years, but a prospective study design with a larger cohort and a longer follow-up is preferred to study aortic growth and associated risk factors. TTE is the most frequently used technique for measuring proximal aortic segments in clinical practice and is an excellent imaging modality for serial measurement of maximal aortic root diameter [28]. But both the TTE investigation and the measurements depend on the operator and the measuring protocol. However, to minimize this bias, the measurements were performed by the same operator who was blinded to the medical history. A control group with women without TS was not available in this study but the growth rate of the ascending aorta was compared with reference values in Caucasians reported by Campens et al. (400 women, >15 years of age with 10 years follow-up) [14]. We measured the aortic dimensions using the inner edge to inner edge principle. In the reference values regarding dimension and growth-rate reported by Campens et al. the leading edge to leading edge principle were used [14]. The leading edge to leading edge method is recommended by AHA and ESC guidelines as it offers better consistency with inner diameters derived from CT or MRI [9,39]. In absolute values, our aortic dimensions will be smaller because the thickness of the aortic wall was not included. However, the difference between baseline and follow-up investigations and assessment of aortic diameter growth will not be affected.

5. Conclusions

The observed aortic growth rate of the ascending aorta in TS was higher than the growth rate in the general female population. Increased body weight, but not the body fat distribution, was the only marker for aortic growth that could be identified in women with TS. Congenital cardiovascular malformations were not predictive of aortic growth. Regular examinations with estimation of the aortic diameter are important in all women with TS.

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CRediT authorship contribution statement

Sofia Thunström: Conceptualization, Data curation, Methodology,

Writing – original draft, Writing – review & editing. **Odd Bech-Hanssen:** Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Emily Krantz:** Writing – original draft, Writing – review & editing. **Inger Bryman:** Supervision, Writing – original draft, Writing – review & editing. **Kerstin Landin-Wilhelmsen:** Funding acquisition, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcchd.2023.100489.

References

[1] Bondy CA. Care of girls and women with turner syndrome: a guideline of the Turner syndrome study group. J Clin Endocrinol Metabol 2007;92:10–25.
[2] Sybert VP, McCauley E. Turner's syndrome. N Engl J Med 2004;351:1227–38.
[3] Schoemaker MJ, Swerdlow AJ, Higgins CD, Wright AF, Jacobs PA. Mortality in women with Turner syndrome in Great Britain: a national cohort study. J Clin Endocrinol Metabol 2008;93:4735–42.
[4] Thunstrom S, Krantz E, Thunstrom E, Hanson C, Bryman I, Landin-Wilhelmsen K. Incidence of aortic dissection in Turner syndrome. Circulation 2019;139:2802–4.
[5] Matura LA, Ho VB, Rosing DR, Bondy CA. Aortic dilatation and dissection in Turner syndrome. Circulation 2007;116:1663–70.
[6] Silaschi M, Byrne J, Wendler O. Aortic dissection: medical, interventional and surgical management. Heart (British Cardiac Society) 2017;103:78–87.
[7] Mortensen KH, Young L, De Backer J, Silberbach M, Collins RT, Duijnhouwer AL, Pandya B, Gravholt CH, Lopez L, Roos-Hesselink JW. Cardiovascular imaging in Turner syndrome: state-of-the-art practice across the lifespan. Heart (British Cardiac Society) 2018;104(22):1823–31.
[8] Gravholt CH, Andersen NH, Conway GS, Dekkers OM, Geffner ME, Klein KO, Lin AE, Mauras N, Quigley CA, Rubin K, Sandberg DE, Sas TCJ, Silberbach M, Soderstrom-Anttila V, Stochholm K, van Alfen-van derVelden JA, Woelfle J, Backeljauw PF. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. Eur J Endocrinol 2017;177:G1–70.
[9] Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H, Evangelista A, Falk V, Frank H, Gaemperli O, Grabenwöger M, Haverich A, Iung B, Manolis AJ, Meijboom F, Nienaber CA, Roffi M, Rousseau H, Sechtem U, Sirnes PA, Allmen RS, Vrints CJ. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). Eur Heart J 2014;35:2873–926.
[10] Mortensen KH, Hjerrild BE, Stochholm K, Andersen NH, Sørensen KE, Lundorf E, Hørlyck A, Pedersen EM, Christiansen JS, Gravholt CH. Dilation of the ascending aorta in Turner syndrome - a prospective cardiovascular magnetic resonance study. J Cardiovasc Magn Reson : official journal of the Society for Cardiovascular Magnetic Resonance 2011;13:24.
[11] Mortensen KH, Wen J, Erlandsen M, Trolle C, Ringgaard S, Gutmark EJ, Gutmark-Little I, Andersen NH, Gravholt CH. Aortic growth rates are not increased in Turner syndrome-a prospective CMR study. European heart journal cardiovascular Imaging 2019;20:1164–70.
[12] Duijnhouwer AL, Bons LR, Timmers H, van Kimmenade RRL, Snoeren M, Timmermans J, van den Hoven AT, Kempers M, van Dijk APJ, Fleischer K, Roos-Hesselink JW. Aortic dilatation and outcome in women with Turner syndrome. Heart (British Cardiac Society) 2018;0:1–8.
[13] Lanzarini L, Larizza D, Prete G, Calcaterra V, Klersy C. Prospective evaluation of aortic dimensions in Turner syndrome: a 2-dimensional echocardiographic study. J Am Soc Echocardiogr 2007;20:307–13. official publication of the American Society of Echocardiography.
[14] Campens L, Demulier L, De Groote K, Vandekerckhove K, De Wolf D, Roman MJ, Devereux RB, De Paepe A, De Backer J. Reference values for echocardiographic assessment of the diameter of the aortic root and ascending aorta spanning all age categories. Am J Cardiol 2014;114:914–20.
[15] Meccanici F, de Bruijn JWC, Dommisse JS, Takkenberg JJM, van den Bosch AE, Roos-Hesselink JW. Prevalence and development of aortic dilation and dissection in women with Turner syndrome: a systematic review and meta-analysis. Expet Rev Cardiovasc Ther 2023;21:133–44.
[16] Thunström S, Thunström E, Naessén S, Berntorp K, Laczna Kitlinski M, Ekman B, Wahlberg J, Bergström I, Bech-Hanssen O, Krantz E, Laine CM, Bryman I, Landin-Wilhelmsen K. Aortic size predicts aortic dissection in Turner syndrome - a 25-year prospective cohort study. Int J Cardiol 2023;373:47–54.
[17] World Medical Association. Declaration of Helsinki ethical principle for medical research involving human subject. Ethical principles for medical research involving human subjects. October, 2008 [Accessed 23 November 2017], https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/doh-oct2008/.
[18] Landin-Wilhelmsen K. Turner syndrome. 2021. https://www.internetmedicin.se.
[19] Saenger P, Wikland KA, Conway GS, Davenport M, Gravholt CH, Hintz R, Hovatta O, Hultcrantz M, Landin-Wilhelmsen K, Lin A, Lippe B, Pasquino AM, Ranke MB, Rosenfeld R, Silberbach M. Recommendations for the diagnosis and management of Turner syndrome. J Clin Endocrinol Metabol 2001;86:3061–9.
[2][0] Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey Jr DE, Eagle KA, Hermann LK, Isselbacher EM, Kazerooni EA, Kouchoukos NT, Lytle BW, Milewicz DM, Reich DL, Sen S, Shinn JA, Svensson LG, Williams DM. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: a report of the American college of cardiology foundation/American Heart association task force on practice guidelines, American association for thoracic surgery, American college of radiology, American stroke association, society of cardiovascular anesthesiologists, society for cardiovascular angiography and interventions, society of interventional radiology, society of thoracic surgeons, and society for vascular medicine. Circulation 2010;121:e266–369.
[21] Meccanici F, Schotte MH, Snoeren M, Bons LR, van den Hoven AT, Kardys I, Budde RPJ, van den Bosch AE, Duijnhouwer AL, Roos-Hesselink JW. Aortic dilation and growth in women with Turner syndrome. Heart (British Cardiac Society) 2022;0:1–9.
[22] Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1989 Nutrition 1916;5:303–11. ; discussion 312-3.
[23] Homer L, Le Martelot MT, Morel F, Amice V, Kerlan V, Collet M, De Braekeleer M. 45,X/46,XX mosaicism below 30% of aneuploidy: clinical implications in adult women from a reproductive medicine unit. Eur J Endocrinol 2010;162:617–23.
[24] Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet (London, England) 1986;1:307–10.
[25] Alberti KG, Zimmet P, Shaw J. Metabolic syndrome–a new world-wide definition. A consensus statement from the international Diabetes federation. Diabet Med : a journal of the British Diabetic Association 2006;23:469–80.
[26] Landin-Wilhelmsen K, Bryman I, Hanson C, Hanson L. Spontaneous pregnancies in a Turner syndrome woman with Y-chromosome mosaicism. J Assist Reprod Genet 2004;21:229–30.
[27] Rodríguez-Palomares JF, Teixidó-Tura G, Galuppo V, Cuéllar H, Laynez A, Gutiérrez L, González-Alujas MT, García-Dorado D, Evangelista A. Multimodality assessment of ascending aortic diameters: comparison of different measurement methods. J Am Soc Echocardiogr 2016;29:819–826.e4. official publication of the American Society of Echocardiography.
[28] Evangelista A, Flachskampf FA, Erbel R, Antonini-Canterin F, Vlachopoulos C, Rocchi G, Sicari R, Nihoyannopoulos P, Zamorano J, Pepi M, Breithardt OA, Plonska-Gosciniak E. Echocardiography in aortic diseases: EAE recommendations for clinical practice. Eur J Echocardiogr : the journal of the Working Group on Echocardiography of the European Society of Cardiology 2010;11:645–58.
[29] Hausleiter J, Meyer T, Hermann F, Hadamitzky M, Krebs M, Gerber TC, McCollough C, Martinoff S, Kastrati A, Schömig A, Achenbach S. Estimated radiation dose associated with cardiac CT angiography. JAMA 2009;301:500–7.
[30] Donadille B, Tuffet S, Cholet C, Nedelcu M, Bourcigaux N, Iserin L, Monnier-Cholley L, Rousseau A, Christin-Maitre S. Prevalence and progression of aortic dilatation in adult patients with Turner syndrome: a cohort study. Eur J Endocrinol 2020;183:463–70.
[31] Landin-Wilhelmsen K, Bryman I, Wilhelmsen L. Cardiac malformations and hypertension, but not metabolic risk factors, are common in Turner syndrome. J Clin Endocrinol Metabol 2001;86:4166–70.
[32] Bondy CA, Van PL, Bakalov VK, Ho VB. Growth hormone treatment and aortic dimensions in Turner syndrome. J Clin Endocrinol Metabol 2006;91:1785–8.
[33] Evangelista A, Sitges M, Jondeau G, Nijveldt R, Pepi M, Cuellar H, Pontone G, Bossone E, Groenink M, Dweck MR, Roos-Hesselink JW, Mazzolai L, van Kimmenade R, Aboyans V, Rodríguez-Palomares J. Multimodality imaging in thoracic aortic diseases: a clinical consensus statement from the European Association of Cardiovascular Imaging and the European Society of Cardiology working group on aorta and peripheral vascular diseases. European heart journal cardiovascular Imaging 2023;24:e65–85.
[34] Lin A, Rajagopalan A, Nguyen HH, White AJ, Vincent AJ, Mottram PM. Dilatation of the ascending aorta in Turner syndrome: influence of bicuspid aortic valve morphology and body composition. Heart Lung Circ 2021;30:e29–36.
[35] De Groote K, Devos D, Van Herck K, Demulier L, Buysse W, De Schepper J, De Wolf D. Abnormal aortic arch morphology in Turner syndrome patients is a risk factor for hypertension. Heart Ves 2015;30:618–25.
[36] Yetman AT, Bisselou KSM, Sanmann JN, Katz RJ, Steingraeber CJ, Wilde M, Murray M, Starr LJ. Vascular dissection in women with Turner syndrome. Int J Cardiol 2021;325:127–31.

[37] LeMaire SA, Russell L. Epidemiology of thoracic aortic dissection. Nat Rev Cardiol 2011;8:103–13.
[38] Carlson M, Airhart N, Lopez L, Silberbach M. Moderate aortic enlargement and bicuspid aortic valve are associated with aortic dissection in Turner syndrome: report of the international turner syndrome aortic dissection registry. Circulation 2012;126:2220–6.
[39] Isselbacher EM, Preventza O, Hamilton Black 3rd J, Augoustides JG, Beck AW, Bolen MA, Braverman AC, Bray BE, Brown-Zimmerman MM, Chen EP, Collins TJ, DeAnda Jr A, Fanola CL, Girardi LN, Hicks CW, Hui DS, Schuyler Jones W, Kalahasti V, Kim KM, Milewicz DM, Oderich GS, Ogbechie L, Promes SB, Gyang Ross E, Schermerhorn ML, Singleton Times S, Tseng EE, Wang GJ, Woo YJ. 2022 ACC/AHA guideline for the diagnosis and management of aortic disease: a report of the American Heart association/American college of cardiology joint committee on clinical practice guidelines. Circulation 2022;146:e334–482.